ORGANIC
LETTERS

2004
Vol. 6, No. 5
715−718

Regioselective Formation of Alkylidenecyclopropanes from 2-Substituted Cyclobutylidenes Generated from Geminal Dibromocyclobutanes and Methyllithium†

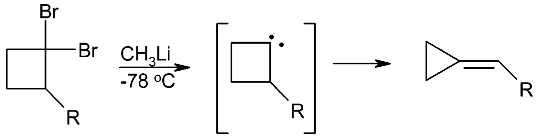
Tore Nordvik, Jean-Luc Mieusset, and Udo H. Brinker*

Institut für Organische Chemie, Universität Wien, Währinger Strasse 38,
A-1090 Wien, Austria

udo.brinker@univie.ac.at

Received December 2, 2003

ABSTRACT



Four different 2-substituted geminal dibromocyclobutanes were reacted with methyllithium at –78 °C. In contrast to previous studies using diazocyclobutanes as carbene precursors at temperatures above 200 °C via reaction of the corresponding tosylhydrazone sodium salts, the organometallic route in each case produces only an alkylidenecyclopropane that could be isolated in good yields. B3LYP calculations were employed to rationalize the observed regioselective ring contraction of the generated cyclobutyliden(oid)s.

Small-ring carbenes, e.g., cyclopropylidenes[1a,b] and cyclobutylidenes,[1c−e] have been used successfully as building blocks in organic synthesis. When compared with cyclopropylidenes, however, much less attention has been paid to cyclobutylidenes. This is clearly due to the more laborious routes involved in the generation of the divalent carbon in four-membered rings.[1c−e,2a] While the alkyllithium reaction with readily available *gem*-dibromocyclopropanes is the most frequently used route to cyclopropyliden(oid)s, the Bamford−Stevens reaction, where a lithium or sodium salt of the cyclobutanone tosylhydrazone is either flash-pyrolyzed or photolyzed, has been the method of choice for the generation of cyclobutylidenes.[1c−e,2] A second approach to liberate cyclobutylidenes from the corresponding diazo compounds has been introduced by Warkentin.[2a,b] Photolysis of oxadiazolines afforded dialkyldiazo compounds. Importantly, the Bamford−Stevens and the alkyllithium reaction differ considerably in their operational temperatures. Thus, while the organometallic route to cyclopropylidenes is usually applied at temperatures below 0 °C, the thermal Bamford−Stevens reaction generally requires temperatures

---

[*] Corresponding author. Phone: +43-1-4277-52121. Fax: +43-1-4277-52140.

[†] Carbene Rearrangements. 59. For Part 58, see: Knoll, W.; Bobek, M. M.; Kalchhauser, H.; Rosenberg, M. G.; Brinker, U. H. *Org. Lett.* **2003**, *5*, 2943.

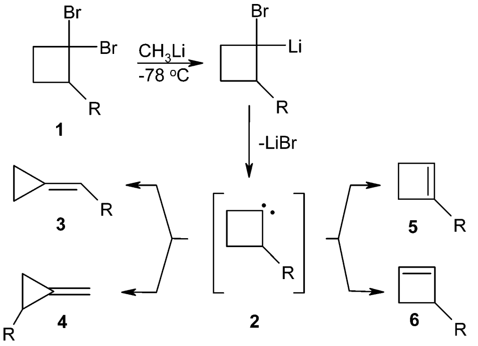
(1) Cyclopropylidenes: (a) Backes, J.; Brinker, U. H. In *Houben-Weyl* (*Methoden der Organischen Chemie*); Regitz, M., Ed.; Thieme: Stuttgart, 1989; Vol. E 19b, pp 391−510. (b) Jones, W. M.; Brinker, U. H. In *Pericyclic Reactions*; Marchand, A. P., Lehr, R. E., Eds.; Academic: New York, 1977; Vol. 1, pp 169−191. Cyclobutylidenes: (c) Backes, J.; Brinker, U. H. In *Houben-Weyl* (*Methoden der Organischen Chemie*); Regitz, M., Ed.; Thieme: Stuttgart, 1989; Vol. E 19b, pp 511−541. (d) Baron, W. J.; DeCamp, M. R.; Hendrick, M. E.; Jones, M., Jr.; Levin, R. H.; Sohn, M. B. In *Carbenes*; Jones, M., Jr., Moss, R. A., Eds.; Wiley: New York, 1973; Vol. 1, pp 42−44. (e) Kirmse, W. In *Carbene Chemistry*, 2nd ed.; Academic: New York, 1971; pp 473−475.

(2) (a) Pezacki, J. P.; Pole, D. L.; Warkentin, J.; Chen, T.; Ford, F.; Toscano, J. P.; Fell, J.; Platz, M. S. *J. Am. Chem. Soc.* **1997**, *119*, 3191. (b) Majchrzak, M. W.; Bézhazi, M.; Tse-Sheepy, I.; Warkentin, J. *J. Org. Chem.* **1989**, *54*, 1842. (c) Brinker, U. H.; Boxberger, M. *Angew. Chem., Int. Ed. Engl.* **1984**, *23*, 974. (d) Brinker, U. H.; Weber, J. *Tetrahedron Lett.* **1986**, *27*, 5371.

10.1021/ol036348r CCC: $27.50

above 200 °C. Only a few examples are known for the generation of cyclobutylidene(oid)s **2** from *gem*-dibromocyclobutanes **1** (Scheme 1) with alkyllithium.[2c,d,4,5]

Scheme 1. Generation and Reaction of 2-Substituted Cyclobutylidenes from Geminal Dibromocyclobutanes



Intramolecular reactions of the parent system **1** (R = H) have been reported to give methylenecyclopropane (**3**) (R = H) and cyclobutene (**5**) (R = H), with the ratio depending on the reaction conditions.[4] Except for a tetracyclic example,[5] intramolecular reactions of 2-substituted *gem*-dibromocyclobutanes are hitherto unknown. Recently, we have developed a more general method for the synthesis of *gem*-dibromocyclobutanes that allows the introduction of substituents at C2.[6] Moreover, nucleoside analogues comprising a (*Z*)- or an (*E*)-alkylidenecyclopropane moiety have been shown recently to be active against human immunodeficiency virus 1 (HIV-1) in vitro.[7] Therefore, a simple low-temperature route to regioselective formation of alkylidenecyclopropanes **3** may be warranted.

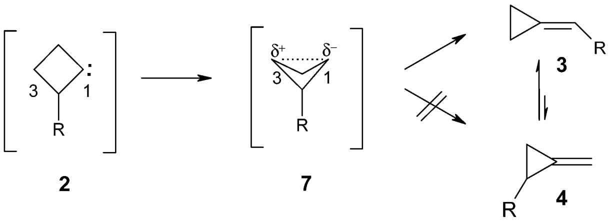
Herein we report on the reactions of four 2-substituted *gem*-dibromocyclobutanes **1a**−**d** with methyllithium that regioselectively afford alkylidenecyclopropanes **3a**−**d** as the sole product in good yields. For cyclobutylidene **2a** (R = *n*-hexyl), we wanted to compare the products from the Bamford−Stevens reaction[8] with those obtained via the organometallic route from the corresponding *gem*-dibromocyclobutane **1a**. We anticipated from both reactions a similar spectrum of primary products. Furthermore, to a small extent, an insertion into the C−H bonds of the side chain could also be expected, since this type of reaction had been observed for the corresponding cyclopropylidenoid generated from the *gem*-dibromocyclopropane with methyllithium.[9] Besides the typical rearrangement to an allene, a 1,5 C−H insertion led to the formation of an entropically favored five-membered ring. Surprisingly, for all systems described here, only compounds **3** could be isolated in good yields (Table 1). No cyclobutenes or products resulting from C−H insertions were found. In sharp contrast, the pyrolysis[10] of the sodium salt of 2-hexylcyclobutanone tosylhydrazone at 240 °C/0.01 Torr afforded a mixture of $C_{10}H_{18}$ products, **3a** (91.9%), **5a**[11] (5.8%), **4a**[12] (1.8%), and a compound found in trace amounts, which according to the ^1H NMR and mass spectrum probably is **6a** (0.4%).

Table 1. Isolated Yields of Alkylidenecyclopropanes **3a**−**d**

entry	R	yield (%)
3a	*n*-hexyl	79
3b	cyclobutylmethyl	75
3c	cyclohexylmethyl	93
3d	benzyl	81

According to early MINDO/3 semiempirical calculations by Schoeller,[13] singlet **2** (R = H) undergoes a ring contraction to **3** (R = H) in a two-step process via a nonclassical bicyclic carbene **7** (R = H) (Scheme 2). Later this rearrangement was reinvestigated at a higher level of theory.[14] Hadad, Platz, and Schaefer III, et al. using Møller−Plesset perturbation as well as hybrid Hartree−Fock/density functional theory methods again predicted singlet cyclobutylidene to possess a nonclassical bicyclic structure.[15] Finally, McMahon and Karney et al. using ab initio (MP2, CCSDCT) and density functional theory (BLYP, B3LYP) calculations confirmed some transannular bonding between the divalent carbon and the opposing CH_2 group in a bicyclobutane-like structure.[16]

Scheme 2. Mechanism of Ring Contraction of 2-Substituted Cyclobutylidenes



---

(3) Friedman, L.; Shechter, H. *J. Am. Chem. Soc.* **1960**, *62*, 1002.

(4) Brinker, U. H.; Schenker, G. *J. Chem. Soc., Chem. Commun.* **1982**, 679.

(5) Jefford, C. W.; Rossier, J.-C.; Zuber, J. A.; Kennard, O.; Cruse, W. B. T. *Tetrahedron Lett.* **1983**, *24*, 181.

(6) (a) Nordvik, T.; Brinker, U. H. *J. Org. Chem.* **2003**, *68*, 9394. (b) Nordvik, T.; Brinker, U. H. *J. Org. Chem.* **2003**, *68*, 7092.

(7) (a) Yoshimura, K.; Feldman, R.; Kodama, E.; Kavlick, M. F.; Qiu, Y.-L.; Zemlicka, J.; Mitsuya, H. *Antimicrob. Agents Chemother.* **1999**, *43*, 2479. (b) Cheng, C.; Shimo, T.; Somekawa, K.; Baba, M. *Tetrahedron* **1998**, *54*, 2031.

(8) For a 2-substituted cyclobutylidene comprising a double bond at C-3 of the side chain generated from the corresponding tosylhydrazone sodium salt, see: Brinker, U. H.; Schrievers, T.; Xu, L. *J. Am. Chem. Soc.* **1990**, *112*, 8609.

(9) Brinker, U. H.; Miebach, T. *J. Org. Chem.* **1999**, *64*, 8000.

(10) Brinker, U. H.; König, L. *Chem. Ber.* **1983**, *116*, 882.

(11) Kasai, K.; Liu, Y.; Hara, R.; Takahashi, T. *Chem. Commun.* **1998**, 1989.

(12) Hsiao, C.-N.; Shechter, H. *J. Org. Chem.* **1988**, *53*, 2688.

(13) Schoeller, W. W. *J. Am. Chem. Soc.* **1979**, *101*, 4811.

(14) Wang, B.-Z.; Deng, C.-H. *Chin. J. Chem.* **1990**, *8*, 102.

(15) Sulzbach, H. M.; Platz, M. S.; Schaefer, H. F., III; Hadad, C. M. *J. Am. Chem. Soc.* **1997**, *119*, 5862.

(16) Stracener, L. L.; Halter, R. J.; McMahon R. J.; Castro, C.; Karney, W. L. *J. Org. Chem.* **2000**, *65*, 199.

The extraordinary structure of cyclobutylidene seems to play an important role for the uncommon preference for the 1,2-C over the competing 1,2-H migration. Moreover, for cyclobutylidene, the triplet−singlet energy gap was calculated to be 5.9 kcal/mol, with the singlet being the ground state.[14]

Computational Methods. The Spartan 02[17] program was used for density functional theory calculations, employing Becke's[18] three-parameter hybrid method and the exchange functional of Lee, Yang, and Parr (B3LYP).[19] The geometry optimizations of the structures were achieved at the HF/3-21G(*) level.[20] Energies were evaluated by using B3LYP/6-31G* single-point calculations. The transition state (TS) geometries obtained with all methods were verified by calculation of their harmonic vibrational frequencies. In the case of the $C_{10}H_{18}$-compounds, the lowest energy conformers were first determined by a conformational search using the semiempirical AM1 model[21] prior to the geometry optimization. Since neither the HF/3-21G(*) nor the B3LYP/6-31G* geometry calculations gave the nonclassical structure **7** (Scheme 2) obtained by higher level calculations,[15,16] the calculations were also performed on 2-methylcyclobutylidene (**2**) (R = CH_3) as a model system at the 6-311+G** level and with Dunning's triple-ζ correlation-consistent basis set, cc-pVTZ.[22] From Table 2 it is obvious that the energy required for **2** (R = CH_3) to reach the transition state (TS) of the ring contraction reaction to **3** (R = CH_3) with 3.2 (cc-pVTZ) and 3.5 kcal/mol (6-31G*), respectively, is the lowest of all competing pathways.

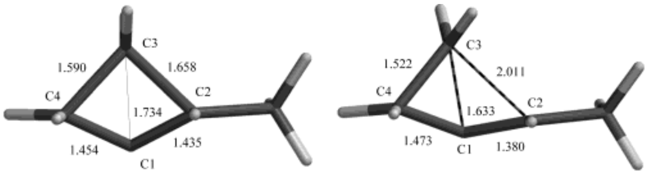
Table 2. Energy Values (kcal/mol) Relative to the Carbene Singlet Ground State for the Transition States

	R = methyl[a]	R = methyl[b]	R = hexyl[b]
exo-bicyclo[2.1.0]pentane	14.2	6.3	4.3
3-R-cyclobutene **6**	12.2	7.0	7.3
alkylmethylenecyclopropane **4**	10	7.3	7.5
endo-bicyclo[2.1.0]pentane			5.9
exo-bicyclo[3.2.0]heptane			5.5
endo-bicyclo[3.2.0]heptane			4.7
1-R-cyclobutene **5**	8.4	2.7	3.5
alkylidenecyclopropane **3**	3.2	3.5	3.8
carbene **2**	0	0	0

[a] B3LYP/cc-pVTZ energies and geometries. [b] B3LYP/6-31G* single-point energy calculations at HF/3-21G(*) geometries.

For 2-hexylcyclobutylidene (**2a**) with 3.8 kcal/mol (6-31G*), a similar value was calculated. In contrast, for the rearrangement of the parent system **2** (R = H) → **3** (R = H), 9.1 kcal/mol (cc-pVTZ) is necessary to reach the TS. Therefore, an alkyl substituent accelerates this rearrangement. For the cyclopropylcarbene−cyclobutene rearrangement, a methyl group was observed to have a similar effect.[23] Since some charge is developed in the TS of the rearrangement, an alkyl group weakens the breaking bond and stabilizes the developing charges.[23] The 1,2-H shift of the tertiary hydrogen atom in 2-methyl-**2** (R = CH_3) and 2-hexylcyclobutylidene (**2a**) to give cyclobutene **5** (R = CH_3) and **5a**, respectively, at the 6-31G* level requires comparable activation energies of 2.7 and 3.5 kcal/mol. At the higher level of theory, however, for 2-methylcyclobutylidene **2** (R = CH_3) an increase to 8.4 kcal/mol was calculated. This is in agreement with the experimental results from the organometallic reaction of **1a** in which no 1-hexylcyclobutene (**5a**) was formed. The alternative ring contraction to the alkylmethylenecyclopropanes **4** (R = CH_3) and **4a** needs an activation energy of 7.3 and 7.5 kcal/mol (6-31G*), respectively, while for the rearrangement **2** → **4** (R = CH_3), 10.0 kcal/mol (cc-pVTZ) are required. These substantially higher energies, when compared with the activation energies for the rearrangement **2** → **3**, explain why **4a** was not observed in the organometallic generation of carbene **2a**. Moreover, intramolecular insertion reactions to give bicyclo[2.1.0]pentanes and bicyclo[3.2.0]heptanes require activation energies in the range of about 5 to 6 kcal/mol.

Finally, at the B3LYP/cc-pVTZ level of theory, the triplet state of methylcyclobutylidene (**2a**) lies 7.6 kcal/mol above the singlet ground state. For the ring contraction **3** → **4**, respectively, at first a bond between C1 and C3 has to be formed leading to the bicyclobutane-like structure **7** (Scheme 2). Next, either the bond between C2 and C3 or C3 and C4 has to break to give **3** and **4**, respectively. In our study, the higher substituted C2−C3 bond is exclusively broken, and concomitantly the C1−C3 bond is established. No methylenecyclopropane **4** could be observed, where the R group is attached to the cyclopropane ring. This experimental result is corroborated by the calculations. Thus, the structure of **2** (R = CH_3) (Figure 1) at the cc-pVTZ level of theory shows already a longer C2−C3 bond (1.66 Å) when compared with the C3−C4 bond (1.59 Å) (Table 3). Moreover, the C1−C2



2 (R=CH_3)

8

Figure 1. Structure of 2-methylcyclobutylidene **2** (R = CH_3) and the transition state **8** that leads to alkylidenecyclopropane **3** (R = CH_3).

---

(17) Kong, J.; White, C. A.; Krylov, A. I.; Sherrill, C. D.; Adamson, R. D.; Furlani, T. R.; Lee, M. S.; Lee, A. M.; Gwaltney, S. R.; Adams, T. R.; Ochsenfeld, C.; Gilbert, A. T. B.; Kedziora, G. S.; Rassolov, V. A.; Maurice, D. R.; Nair, N.; Shao, Y.; Besley, N. A.; Maslen, P. E.; Dombroski, J. P.; Daschel, H.; Zhang, W.; Korambath, P. P.; Baker, J.; Byrd, E. F. C.; Van Voorhis, T.; Oumi, M.; Hirata, S.; Hsu, C.-P.; Ishikawa, N.; Florian, J.; Warshel, A.; Johnson, B. G.; Gill, P. M. W.; Head-Gordon, M.; Pople, J. A. *J. Comput. Chem.* **2000**, *21*, 1532.

(18) Becke, A. D. *J. Chem. Phys.* **1993**, *98*, 5648.

(19) Lee, C.; Yang, W.; Parr, R. G. *Phys. Rev. B* **1988**, *37*, 785.

(20) Binkley, J. S.; Pople, J. A.; Hehre, W. J. *J. Am. Chem. Soc.* **1980**, *102*, 939.

(21) Dewar, M. J. S.; Zoebisch, E. G.; Healy, E. F.; Stewart, J. J. P. *J. Am. Chem. Soc.* **1985**, *107*, 3902.

(22) Dunning, T. H., Jr. *J. Chem. Phys.* **1989**, *90*, 1007.

Table 3. Bond Lengths and Dihedral Angles for 2-Hexyl- and 2-Methylcyclobutylidene **2a** and **2** (R = CH_3), the Transition State Structure **8**, and Alkylidenecyclopropane **3** (R = CH_3)

	hexyl	methyl	methyl	methyl	**8**	**3** (R = CH_3)
	cc-pVTZ[a]	cc-pVTZ[a]	6-311+G**[a]	6-31G*[a]	cc-pVTZ[a]	cc-pVTZ[a]
C1−C2	1.437	1.435	1.445	1.535	1.380	1.318
C2−C3	1.651	1.658	1.646	1.556	2.011	2.675
C3−C4	1.593	1.590	1.599	1.550	1.522	1.539
C1−C4	1.453	1.454	1.458	1.519	1.473	1.462
C1−C3	1.737	1.734	1.752	2.214	1.633	1.465
dihedral angle C1−C2−C3−C4	38.2	38.4	38.1	14.6	46.1	

[a] B3LYP calculations.

bond is slightly shorter than the C1−C4 bond. Since in **2** (R = CH_3) the C2−C3 bond eventually has to be broken and the C1−C2 bond has to become the double bond in **3** (R = CH_3), this is even more pronounced in the TS structure **8**. With 1.38 Å, the C1−C2 bond now has almost reached the final length of the double bond of the product, ethylidenecyclopropane (**3**) (R = CH_3), while the distance between C2 and C3 is further elongated to 2.01 Å.

As expected, with a distance of 1.63 Å, the central C1−C3 bond of the nonclassical bicyclic carbene **2** (R = CH_3), when compared with that of the TS structure **8**, has been further shortened during its transformation to a lateral cyclopropane bond of **3** (R = CH_3).

It has been shown that alkylidenenecyclopropanes **3** are the secondary thermal products of **4**.[24] In this study, this would require, however, that the rearrangement **4** → **3** had taken place already at temperatures as low as −78 °C during the reaction, at workup at about 0 °C, or at distillation temperatures (20−50 °C). As has been observed (vide supra), the reactions of **1** with methyllithium afforded exclusively **3**. Since the rearrangement **4** → **3** demands temperatures of about 150 °C,[24] the firsthand formation of methylenecyclopropanes **4** from **2**, under the reaction conditions applied in our study, is highly unlikely.

In conclusion, we have shown that the methyllithium reaction of 2-substituted *gem*-dibromocyclobutanes **1** in all cases gives only *one* product, i.e., alkylidenecyclopropanes **3**. This is in stark contrast to systems previously studied, where under Bamford−Stevens reaction conditions *both* possible ring contraction products were always observed. Moreover, in the organometallic approach presented here, no cyclobutenes or the corresponding ring-opened products, i.e., 1,3-butadienes, were found. This is markedly different from the reaction of the parent 1,1-dibromocyclobutane (**1**) (R = H), where also cyclobutene (**5**) (R = H) could be isolated in yields up to 17%.[4]

Acknowledgment. Dedicated to Professor Manfred T. Reetz on the occasion of his 60th birthday. We thank Ms. S. Felsinger and Ms. C. Tyl for the recording of 400 MHz ^1H and 100 MHz ^{13}C NMR spectra and Ms. M. Pacar for technical assistance.

Supporting Information Available: Energy values for the products of **2a** and **2** (R = CH_3) and ^1H and ^{13}C NMR spectra of compounds **3a−d** and of 2-hexylcyclobutanone tosylhydrazone. This material is available free of charge via the Internet at http://pubs.acs.org.

OL036348R

---

[23] Thamattoor, D. M.; Snoonian, J. R.; Sulzbach, H. M.; Hadad, C. M. *J. Org. Chem.* **1999**, *64*, 5886.

[24] Gajewski, J. J. *Hydrocarbon Thermal Isomerizations*; Academic: New York, 1981; pp 51−61.